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Treatment of Smith–Lemli–Opitz Syndrome: Results of a Multicenter Trial

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Patients with the RSH or Smith–Lemli–Opitz syndrome (SLOS) have an inborn error of cholesterol biosynthesis which results in a deficiency of cholesterol and an elevation of the cholesterol precursor, 7-dehydrocholesterol. A treatment protocol consisting of administration of cholesterol ± bile acids was initiated in an attempt to correct the biochemical abnormalities seen. Fourteen patients (8 female, 6 male: ages 2 months to 15 years) have now been treated for 6–15 months. Three patients received cholesterol alone, while 11 patients received cholesterol and one or more bile acids. Biochemical improvement in sterol levels and in the ratio of cholesterol to total sterols was noted in all patients. The most marked improvement was noted in patients presenting with initial cholesterol levels <40 mg/dl. No toxicity was observed. Clinical improvement in growth and neurodevelopmental status was also observed. Am. J. Med. Genet. 68:311–314, 1997.

KEY WORDS: Smith–Lemli–Opitz syndrome; cholesterol; sterol metabolism bile acids; treatment

INTRODUCTION

The RSH or Smith–Lemli–Opitz syndrome (SLOS) is an autosomal recessive syndrome first described in 1964 characterized by growth and developmental retardation and multiple anomalies [Smith et al., 1964]. In 1993, we reported an abnormality in cholesterol metabolism in affected patients [Irons et al., 1993; Tint et al., 1994], and deficiency of the enzyme 7-dehydrocholesterol reductase was established recently [Shefer et al., 1995]. Affected patients have decreased cholesterol levels and increased levels of the immediate precursor, 7-dehydrocholesterol (7-DHC) and its isomer, 8-dehydrocholesterol (8-DHC).

Shortly after discovery of the cholesterol deficiency in affected patients, a treatment protocol was devised to correct the metabolic abnormalities present [Irons et al., 1994]. The goal of this protocol was to raise serum cholesterol levels, while lowering levels of the cholesterol precursors, 7-DHC and 8-DHC, thus increasing the ratio of cholesterol to total sterols (ratio C/S). The therapy consisted of supplying cholesterol in a dose of approximately 60–120 mg/kg/day, in combination with one or more bile acids to correct the bile acid deficiency. Bile acids were also useful in facilitating cholesterol absorption. The cholesterol was supplied either as a suspension of pharmaceutical grade cholesterol in soy oil, or as food, usually egg yolks. The bile acids used included ursodeoxycholic acid (15 mg/kg/day), with or without chenodeoxycholic acid (7 mg/kg/day) when it was commercially available.

The goals of the treatment protocol were to determine whether supplying exogenous cholesterol with or without bile acids would correct the sterol biochemical abnormalities in affected patients, and whether correction of these biochemical abnormalities would lead to improved growth and neurodevelopmental outcome.

MATERIALS AND METHODS

Fourteen patients with SLOS were treated at 7 medical centers in the United States. All were confirmed to have the biochemical abnormalities (low plasma cholesterol, elevated 7-DHC and 8-DHC) seen in affected patients.

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Eleven patients were treated with a combination of cholesterol and bile acid(s). This group includes 6 girls, age 2 months to 12.7 years at entry, with pretreatment cholesterol levels ranging from 8 to 58 mg/dl, and 5 boys, age 6 months to 14.5 years at entry, with pretreatment cholesterol levels of 38 to 80 mg/dl. Nine patients in this group received cholesterol in the form of a cholesterol suspension, while 2 received their cholesterol in the form of egg yolks. Cholesterol intake ranged from approximately 40–120 mg/kg/day over the course of the treatment period. Six patients received ursodeoxycholic acid as the only bile acid used, while 5 others received chenodeoxycholic acid in addition to the ursodeoxycholic acid while it was commercially available. This group has been treated from 6 to 18 months, with one patient treated for only 3 months thus far.

Three patients were treated with cholesterol alone at the request of their parents and physician. This group includes two sibs, age 2 months and 2.5 years, whose initial cholesterol levels were 18 and 33 mg/dl. Another girl, age 15 years, with an initial level of 83 mg/dl, also is in this group. These children have been treated from 6 to 16 months.

Plasma sterol levels were monitored regularly, as well as urine and stool bile acids. Measures of bone marrow (cbc, platelet count), liver (SGOT, SGPT), and renal (BUN, creatinine) function are monitored several times per year. Growth parameters, physical and neurologic findings, and measures of developmental and neuropsychological function are also monitored prospectively.

RESULTS

Cholesterol levels and the ratio of cholesterol to total sterols (ratio C/S) rose in all patients treated, although to varying levels and by varying degrees. This is shown in Figures 1 and 2 indicating plasma cholesterol levels and ratio C/S at 6 months of therapy compared with levels at entry in 12 patients who had been treated for at least 6 months.

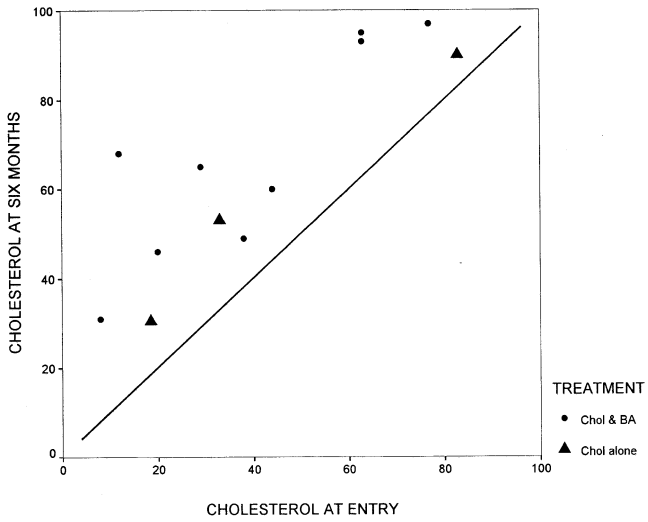

Fig. 1. Plot of plasma cholesterol (mg/dl) at entry against cholesterol at 6 months of therapy in 12 patients treated at least 6 months.

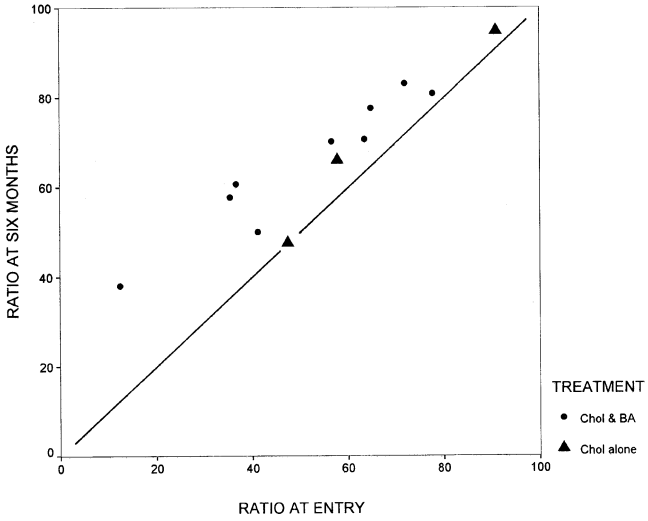

Fig. 2. Plot of the ratio of plasma cholesterol to total sterols (%) at entry against this ratio at 6 months of therapy in 12 patients treated at least 6 months.

In the 11 patients treated with a combination of cholesterol and bile acid(s), cholesterol levels have increased in all but one (Fig. 3). This patient's cholesterol level dropped from 95 to 76 mg/dl on therapy, but this was associated with an increase in weight and height. The ratio of cholesterol to total sterols also increased, but less than the increase in cholesterol levels (Fig. 4). The data are presented in Table I.

Examined numerically, the average percentage change in plasma cholesterol in all patients in this group was 131%, or 16% per month to adjust for the different lengths of therapy. The change in the ratio C/S was 55%, or 6.1% per month. The greatest percentage change occurred in the patients whose initial cholesterol levels were below 40 mg/dl. The change in cholesterol in this group was 235%, and the change in the ratio C/S was 101.7%.

In the 3 patients treated with cholesterol alone, cholesterol levels and the ratio C/S also increased (Figs. 5 and 6). The data for these children are presented in Table II.

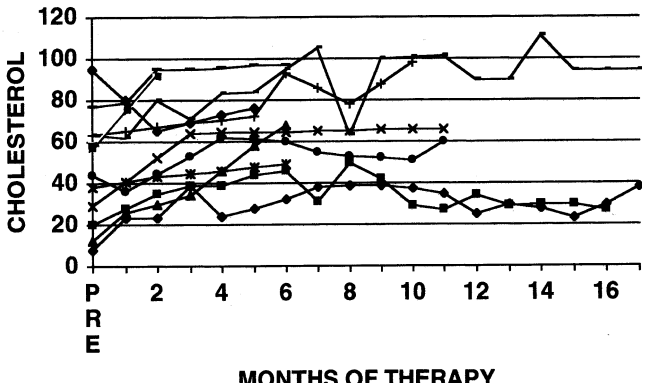

Fig. 3. Plasma cholesterol levels (mg/dl) on therapy in patients receiving cholesterol and bile acid(s).

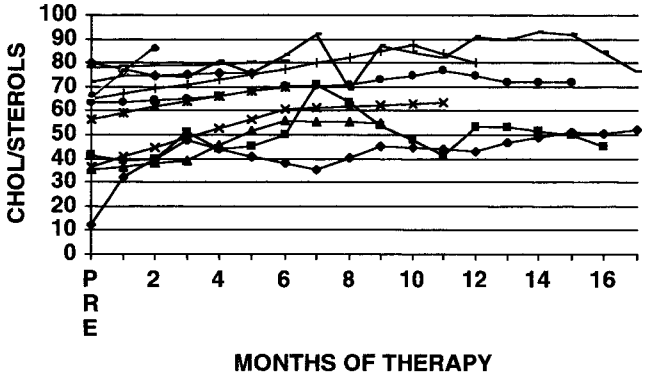

Fig. 4. Ratio of cholesterol to total sterols (%) on therapy in patients receiving cholesterol and bile acid(s).

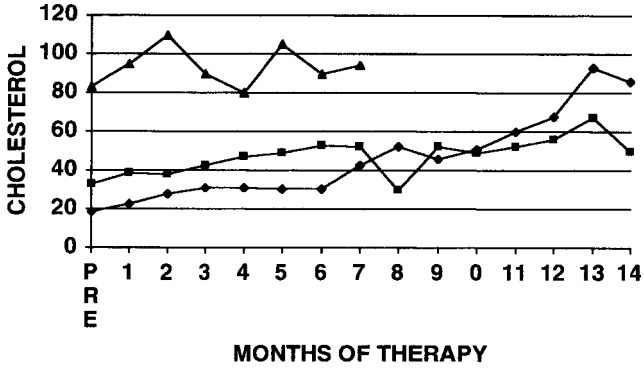

Fig. 5. Plasma cholesterol levels (mg/dl) on therapy in patients receiving cholesterol alone.

The average change in plasma cholesterol was 163.5%, or 10.6% per month, and the average change in the ratio was 38.5%, or 2.5% per month. Once again, the greatest average change occurred in the children with initial levels below 40 mg/dl. The change in cholesterol and the ratio C/S in these two children was 238.7 and 55.5%, respectively.

The difference in the magnitude of rise in plasma cholesterol and the ratio C/S is not statistically significant between the two treatment groups.

Our experience with discontinuation of bile acids in several patients has taught us something about the effect of bile acid supplementation. One patient will be used to exemplify this point. Figure 7 is a graph of plasma cholesterol levels in the first patient identified to have the metabolic defect. Her pretreatment cholesterol level was 8 mg/dl and treatment was begun with cholesterol, ursodeoxycholic acid, and chenodeoxycholic acid. Her cholesterol levels increased to 39 mg/dl by 10 months. At 11 months of therapy, her chenodeoxycholic acid was discontinued because it was no longer available in the United States. Her plasma cholesterol levels slowly decreased over the next several months to 23 mg/dl at 15 months. Her ursodeoxycholic acid was then discontinued. After discontinuation of the ursodeoxycholic acid, her cholesterol levels rose to 42 mg/dl on cholesterol alone. This same phenomenon was also demonstrated in another patient in our care.

TABLE I. Percentage Change RX: Cholesterol + Bile Acids

Patient sex; age (years)	Ratio (pre-On Rx)	% Change	Chol level (pre-On Rx)	% Change
F; .5	12–47	292	8–39	387.5
F; 12.6	41–63	53.6	20–50	150
F; .8	33–55.1	67	12–70	483.3
F; 3.8	37–64	73	29–66	127.6
M; 14.5	57–70	22.8	38–49	29
M; 9.5	64–72	12.5	44–60	36.4
F; 13	65–87	33.8	58–91	57
M; 3.8	65–80	23	63–118	87.3
F; 5.8	72–93	29.2	63–111	76.2
M; 15.8	78–81	3.9	77–97	26
M; 1	80–76	−5	95–76	−20

DISCUSSION

As indicated in the preceding section, treatment with cholesterol with or without bile acid(s) can improve the sterol abnormalities seen in patients with the SLOS. The degree of improvement varies between patients, and may depend on the degree of biochemical abnormality present. Many of the patients with the lowest cholesterol levels prior to therapy still have levels below normal (<100 mg/dl) on treatment. Further treatment with possibly higher levels of cholesterol will be needed to determine if cholesterol levels can be increased to the normal range. While we have raised the ratio C/S, we have not been able to eliminate the cholesterol precursors, 7-DHC and 8-DHC. Once again, higher doses of cholesterol might be needed to decrease endogenous cholesterol synthesis.

There also appears to be no benefit to supplementation with bile acids, as the degree of improvement in sterol levels was not statistically significant in the patients treated with bile acids and those without. In addition, it appears that treatment with ursodeoxycholic acid, at least in some patients, might lead to lower cholesterol levels on treatment, possibly by interfering with cholesterol absorption.

The therapy has been well tolerated by all patients thus far with no signs of toxicity. Growth in all patients

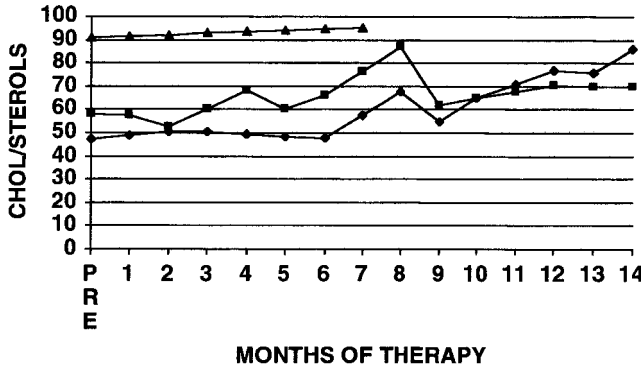

Fig. 6. Ratio of cholesterol to total sterols (%) on therapy in patients receiving cholesterol alone.

TABLE II. Percentage Change RX: Cholesterol Alone

Patient sex; age (years)	Ratio (pre-On Rx)	% Change	Cholesterol (pre-On Rx)	% Change
F; 1.7	44–83	88.6	18–93	416.7
M; 3.3	58–71	22.4	33–53	60.6
F; 15.8	91–95	4.4	83–94	13.2

has continued slowly, some at faster rates than others, although many of the younger patients with the lowest cholesterol levels are still at less than the 5th centile for all growth parameters (weight, height, and head circumference). There appears to be no correlation between degree of change in plasma sterol levels and growth. Some patients with the smallest degree of change in plasma sterol levels have experienced the greatest increase in growth rate.

However, some of the older patients have shown remarkable increases in growth. One patient recently seen in Boston and started on therapy exemplifies this phenomenon. This 14-year-old boy has gained 3.5 kg and grown 9.5 cm in the first 3 months of therapy with the cholesterol suspension. His cholesterol level has risen from 42 to 72 mg/dl. His head circumference has grown 2 cm in the same time period. He has started walking independently and is much more aware of his environment. He has started to explore his home and open and close closet doors, which he was never previously interested in doing. There has also been a decrease in self-abusive behavior.

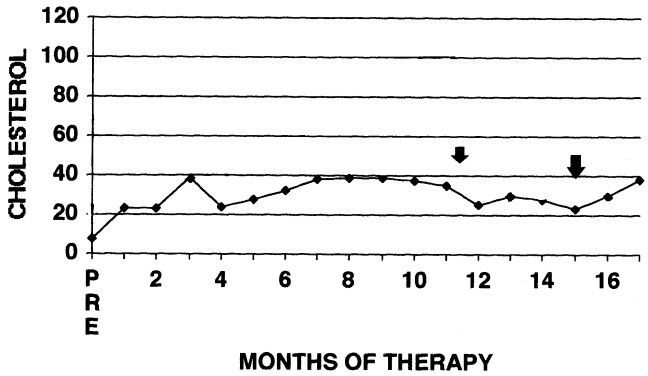

Fig. 7. Plasma cholesterol levels (mg/dl) in one patient receiving cholesterol and bile acids. The chenodeoxycholic acid was discontinued at 11 months (first arrow) and the ursodeoxycholic acid was discontinued at 15 months (second arrow).

Whether or not this therapy will effect a change in neurodevelopmental status is more difficult to say at this time, as the treatment period has been relatively short and the ages and degree of metabolic defects in the treated patients are too diverse. Preliminary objective neurodevelopmental data, which we think indicate that this therapy is of benefit to children at all ages, are presented in the paper by Elias et al. in this issue.

Subjectively, parents and teachers note that the children are more alert, happier, and stronger. There has been a noticeable decrease in self-abusive behavior in the older children. Other areas of improvement include a decrease in photosensitivity and hearing impairment.

In conclusion, cholesterol treatment with or without bile acids can alter the plasma sterol profiles in patient with the SLOS. The greatest change in cholesterol levels occurs in patients with the lowest pretreatment levels. Clinical improvement in growth and development has been noted.

More patients with this syndrome will need to be treated for longer periods of time and more data with regards to the effect of this treatment regimen on growth and neurodevelopmental status will be needed to determine the true benefit of this therapy.

ACKNOWLEDGMENTS

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REFERENCES

Irons M, Elias ER, Salen G, Tint GS, Batta AK (1993): Defective cholesterol biosynthesis in Smith-Lemli-Opitz syndrome. Lancet 341:1414.

Irons M, Elias ER, Tint GS, Salen G, Frieden R, Buie TM, Ampola M (1994): Abnormal cholesterol metabolism in the Smith-Lemli-Opitz syndrome: Report on clinical and biochemical findings in four patients and treatment in one patient. Am J Med Genet 50:347–352.

Shefer S, Salen G, Batta AK, Honda A, Tint GS, Irons M, Elias ER, Chen TC, Holick MF (1995): Markedly inhibited 7-dehydrocholesterol-delta 7-reductase activity in liver microsomes from Smith-Lemli-Opitz homozygotes. J Clin Invest 96:1779–1785.

Smith DW, Lemli R, Opitz JM (1964): A newly recognized syndrome of multiple congenital anomalies. J Pediatr 64:210–217.

Tint GS, Irons M, Elias ER, Batta AK, Frieden R, Chen TS, Salen G (1994): Defective cholesterol biosynthesis associated with the Smith-Lemli-Opitz syndrome. N Engl J Med 330:107–113.